National Cancer Institute Best Practices for Biospecimen Resources

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BACKGROUND

The NCI defines a biospecimen resource as a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all relevant processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer. Biospecimen resources are critical to the research community to support genomic- and proteomic-based cancer research because high-quality biospecimens and data are necessary to understand disease mechanisms at the molecular level. As a step toward achieving the highest possible biospecimen quality and fulfilling the Institute's goal of funding the highest quality research, the NCI is calling for the voluntary implementation of the NCI Best Practices for Biospecimen Resources (formerly the First-Generation Guidelines for NCI-Supported Biorepositories, or "Guidelines"). These recommendations identify best practices for biospecimen collection, processing, storage, retrieval, and dissemination and address concepts of good laboratory practice to encourage a level of consistency and standardization across NCI-supported biospecimen resources.

The NCI Best Practices development process was initiated by the NCI through a multiyear undertaking that began in 2002, including a 2004 presentation to the National Cancer Advisory Board (NCAB) of a study that showed substantial heterogeneity in biospecimen resource management practices across NCI-supported biospecimen resources (NCAB 2004). The 125 programs included in the study support basic, epidemiologic, translational, and clinical research, and most collect frozen biospecimens and support genomic and proteomic research. In fiscal year 2003, approximately 4 million human specimens were collected, maintained, and/or stored by these programs. On an annual basis, the NCI invests more than $50 million in biospecimen resource programs, not including biospecimen resources supported through individual investigator grants such as R01s. This study also revealed that NCI-supported biospecimen resources are not optimized in terms of operational, legal, and ethical policies and procedures, nor are they coordinated to provide a unique resource value. Specifically, it showed that:

- There are no common standard operating procedures (SOPs) or quality assurance/quality control (QA/QC) measures across the broad range of programs.
- The programs lack a common database.
- There is no consistent, defined mechanism to access NCI-supported biospecimen resources.

In 2005 the NCI took several actions approved by the NCAB to respond to these findings, including (1) the establishment of the Biorepository Coordinating Committee (BCC) and (2) the development of the First-Generation Guidelines for NCI-Supported Biorepositories in the interest of ensuring sufficient biospecimens of documented quality to support NCI-sponsored research and the findings that guide the scientific policy of the NCI. The BCC is advisory to the NCI's Office of Biorepositories and Biospecimen Research (OBBR). The primary purpose of the BCC is to work with the OBBR to coordinate the NCI's biospecimen resources in a manner that optimizes the quality and accessibility of biospecimens for the broad cancer research community.

Toward this goal, the OBBR and the BCC organized two workshops during summer 2005 to inform the development of specific recommendations. These workshops, which were based on the development of a series of white papers that consolidated documents and the overall knowledge base in biospecimens, brought together diverse representatives from the cancer research community as well as ethics, policy, and legal experts to discuss and propose approaches that could help unify, integrate, and improve NCI-supported biorepository activities. The recommendations that resulted from the workshops are summarized in the report "Harmonizing Processes and Policies for NCI-Supported Biorepositories,"[1] which was presented to the NCAB in September 2005. This report as well as additional NCI-sponsored

[1] http://biospecimens.cancer.gov/biorepositories/bcc_summary.asp

meetings and work conducted between 2002 and 2005, formed the basis of the First-Generation Guidelines for NCI-Supported Biorepositories.

The Guidelines were published in the Federal Register on April 28, 2006 (71 FR 25184) and were posted on the Web site of the NCI OBBR.[2] The NCI requested public comments on the Guidelines through the Federal Register posting and the OBBR Web site. The public comment period, originally set for a period of 30 days, was extended an additional 30 days through July 3, 2006.

The NCI received public comments from 61 respondents including individuals and groups representing academic institutions, professional societies, private industry, healthcare systems, foundations, advocacy groups, and Federal Government agencies. Representatives of cancer centers and biospecimen resources constituted the majority of the respondents. The responses received ranged from general comments to detailed reviews of the Guidelines.

The Guidelines, now titled NCI Best Practices for Biospecimen Resources, have been revised based on input from these respondents, summarized below, and content experts. The NCI acknowledges that with the emergence of new scientific developments, technologies, and clinical practices and ethical and legal policies and regulations (including NIH and Department of Health and Human Services policies), future generations of the NCI Best Practices will need to be developed with additional input from researchers, biospecimen resource managers, advocates, policymakers, and related stakeholders. Recommended modifications to the NCI Best Practices will be considered by the NCAB.

[2] http://biospecimens.cancer.gov/biorepositories/First%20Generation%20Guidelines%20042006.pdf

NATIONAL CANCER INSTITUTE
BEST PRACTICES FOR BIOSPECIMEN RESOURCES

A. Scope, Applicability, and Implementation

A.1. Scope

This document identifies best practices for biospecimen collection, processing, storage, retrieval, and dissemination and addresses concepts of good laboratory practice to ensure a level of consistency and standardization across National Cancer Institute (NCI)-supported biospecimen resources. A biospecimen resource is defined as a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all relevant processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer.

A.2. Applicability

The implementation of the NCI Best Practices is voluntary, and several recommendations in the NCI Best Practices can be broadly or narrowly applied depending on the mission of the biospecimen resource and/or the study design.

A.3. Implementation

A.3.1. Educational Outreach Program

An educational outreach program will be launched by the NCI in 2007. As part of this outreach program, several public meetings will be held across the United States to inform members of the intramural and extramural research communities about the NCI Best Practices and provide a forum for questions and feedback.

A.3.2. Biospecimen Resources

Biospecimen resources are encouraged to consider the NCI Best Practices in their biospecimen management plan.

B. Technical and Operational Best Practices

B.1. Biospecimen Collection, Processing, Storage, Retrieval, and Dissemination

Although the specific mission of a biospecimen resource will result in the use of different collection and processing procedures, common principles should apply to all biospecimen types. The best practices below are based on current, published information and will be revised periodically as new information is generated from ongoing research projects.[3]

[3] Recognizing the importance of moving toward evidence-based standards for the collection, storage, and analysis of biospecimens, the NCI recently launched the Biospecimen Research Network (BRN). The BRN comprises intramural, extramural, military, and industrial clinical centers and research laboratories that will provide and analyze specimens to determine how the results of DNA, RNA, and protein analyses are affected by pre-acquisition and post-acquisition variables. The results of the BRN research will help inform future generations of guidelines for NCI-supported biospecimen resources and move toward the development of evidence-based standard operating procedures that are both specimen specific and analysis platform specific. Data generated by the BRN will be available to the scientific research community through a searchable, Web-based tool. (For more information about the BRN, see http://biospecimens.cancer.gov/sciences/symposium.asp.)

B.1.1. Determining Which Biospecimens To Collect

B.1.1.1. Collection priorities should be based on the defined purpose of each NCI-supported biospecimen resource in supporting specific types of research.

B.1.1.2. Biospecimens should be collected from populations with demographic characteristics and diversity appropriate to the scientific goals of the research.

B.1.2. Biospecimen Collection and Processing

Biospecimen collection occurs in many contexts, including surgical procedures, organ donation and transplantation, autopsies, and venipuncture; for population-based studies, collection may occur in field locations such as hospitals or research participants'[4] homes (Eiseman and Haga 1999).

B.1.2.1. In the future, the NCI will provide guidance on biospecimen collection while allowing for flexibility when new methodologies are warranted. This guidance will include:

- Collection protocols for various biospecimen types based on solid research data
- Uniform, nonredundant sample nomenclature across NCI-sponsored biospecimen resources
- Comprehensive sample tracking procedures and supporting informatics using state-of-the-art technology whenever possible
- A quality management system (QMS) to promote adherence to best practices

In addition, a high level of biospecimen annotation will be recommended. This will involve consistently recording key data across NCI-sponsored biospecimen resources. Appropriate and complete documentation surrounding biospecimen collection, processing, and storage is essential and relevant to the quality of research data to be obtained.

B.1.2.2. Biospecimen resources should record all data relevant and necessary to research goals, including the collection and processing procedures used.[5]

- For solid tissue biospecimens, the time for collection should be minimized as much as possible; biospecimen temperature should be reduced as soon as possible after collection. Biospecimen processing time should be minimized if freezing is the stabilization endpoint.
- Rapid processing may not be as critical for other types of biospecimens, such as blood, and optimal processing times may vary depending on the analysis method for which a biospecimen is used.

[4] While the NCI views the terms "research participant" and "human subject" as equivalent, the latter term is used when discussing the regulation at 45 CFR Part 46 Subpart A (the Common Rule).

[5] The NCI will support research to determine the effects of various biospecimen processing methods on analyte preservation. Biospecimen resources should continually attempt to improve collection and processing methods to maximize the quality of materials for molecular analysis. NCI-supported biospecimen resources should document the effects of different processing methods and develop guidelines for biospecimen processing based on the goal of preserving various analytes.

B.1.2.3. NCI-supported biospecimen resources should seek to use the processing method that preserves the greatest number of analytes, unless the aim of a particular study specifically requires alternative processing.

B.1.3. Biospecimen Resource Personnel

Personnel involved in biospecimen resource management and use, including researchers, technicians, nurses, surgeons, pathologists, anesthesiologists, and assistants, should be aware of the purpose and goals of the biospecimen resource. To ensure the collection of high-quality biospecimens for research, collection, and processing, personnel should be well qualified and trained to adhere to applicable standard operating procedures (SOPs). A pathologist or his/her designee should be involved for expertise in collecting and processing surgical and autopsy biospecimens. It is important that a pathologist determine what biospecimen is necessary for pathologic diagnosis and what is excess and can be given to the biospecimen resource for research purposes. This is crucial in ensuring that patient care is not compromised.

B.1.4. Biospecimen Storage

The following general best practices apply to all types of biospecimens, such as wet tissue, frozen tissue, paraffin-embedded tissue, glass slides, blood, serum, and urine. Individual types of biospecimens should be handled according to SOPs specific to each biospecimen type and to the biomolecules to be analyzed in that biospecimen type (e.g., ribonucleic acid [RNA], deoxyribonucleic acid [DNA], protein, lipid, etc.).

B.1.4.1. Standardized protocols should be applied consistently in preparing and storing biospecimens to ensure their quality and to avoid introducing variables into research studies. Biospecimen resource personnel should record storage conditions and especially deviations from SOPs, including information about temperature, thaw/refreeze episodes, and equipment failures (International Society for Biological and Environmental Repositories [ISBER] 2005, Mager et al. 2004).

B.1.4.2. Biospecimens should be stored in a stabilized state. A biospecimen resource should avoid unnecessary thawing and refreezing of frozen biospecimens or frozen samples of biomolecules extracted from the biospecimens, and appropriate size aliquots and samples should be used to avoid thawing and refreezing of biospecimens.

In selecting biospecimen storage temperature, biospecimen resources should consider the biospecimen type, the anticipated length of storage, the biomolecules of interest, and whether study goals include preserving viable cells (Hayes et al. 2002, ISBER 2005, Holland et al. 2003).

B.1.4.3. Storage vessels should be stable under planned storage conditions (Caporaso and Vaught 2002, Grizzle 2004). Biospecimen containers should be chosen with analytical goals in mind.

B.1.4.4. Each storage container should have a unique identifier (or combination of identifiers that makes the biospecimen unique) for the biospecimen aliquot that is firmly affixed to the container, clearly and legibly marked, and able to endure storage conditions. All other relevant information should be tied to this identifier, bearing in mind research participant confidentiality, security, and informed consent provisions. Inventory systems should relate the presence of

each aliquot to its specific position in a specific freezer, refrigerator, or shelf. This recommendation applies primarily to biospecimen collections established after publication of this document.

B.1.4.5. Automated security systems should continuously monitor the function of storage equipment. Backup equipment, such as an alternative power source, should be automatically activated when necessary. Emergency procedures should be in place to respond to freezer failures, weather emergencies, and other emergency situations (Friede et al. 2003, Landi and Caporaso 1997, Caporaso and Vaught 2002, Eiseman et al. 2003).

B.1.5. Shipping Samples

B.1.5.1. Retrieval. Samples should be retrieved from storage according to biospecimen resource SOPs that safeguard sample quality.

B.1.5.2. Shipping conditions. When seeking to regulate sample temperature during shipping, consider the shipping time, distance, climate, season, method of transportation, and regulations as well as the type of samples and their intended use (Landi and Caporaso 1997, ISBER 2005).

B.1.5.3. Documentation. The biospecimen resource should notify a recipient before shipping to confirm that the recipient can accept the package and properly store the samples. A shipping log, either written or computerized, should track shipments from and to the biospecimen resource (ISBER 2005).

B.1.5.4. Regulatory considerations. Consult ISBER Best Practices and International Air Transport Association (IATA) regulations (ISBER 2005, IATA 2006) for information concerning international transport regulations and classifying samples for shipment. Variation in national and regional standards regarding biospecimen transport should be considered when shipping biospecimens to or from an international location.

Consult Occupational Safety and Health Administration (OSHA) regulations on toxic and hazardous substances (29 CFR 1910 Subpart Z) to determine whether a substance requires a biohazard label.

B.1.5.5. Training. Training of personnel for shipment of samples is strongly recommended (ISBER 2005).

B.2. Collecting and Managing Clinical Data

Appropriate annotation of biospecimens is crucial to the overall usefulness of the biospecimen resource as a tool for scientific research (Eiseman et al. 2003). Biospecimen resources store biospecimens collected using multiple methodologies and procedures. Researchers rely on banked biospecimens for a wide variety of purposes, including target discovery and validation, prevention research, research on early detection, genetic studies, and epidemiologic analyses. The data recorded by investigators and biospecimen resources depend on the types of biospecimens collected and the studies' objectives.

B.2.1. Collecting Clinical Data

B.2.1.1. NCI-supported biospecimen resources should strive to collect and store all pertinent clinical data associated with a biospecimen if permitted by the study

design and research participant authorization. The NCI recognizes that data collection is not always the responsibility of the biospecimen resource.

B.2.1.2. Data collection activities should conform to U.S. Food and Drug Administration (FDA) requirements (see 21 CFR Part 11 or the FDA guidance document at http://www.fda.gov/ora/compliance_ref/part11/), if and where applicable, so that the data can be cited and/or used in Investigational New Drug and Investigational Device Exemption applications.

B.2.1.3. NCI-supported biospecimen resources should employ a uniform, nonredundant vocabulary (e.g., cancer Biomedical Informatics Grid [caBIG™] common data elements [CDEs]) for clinical data across sponsored biospecimen resources.

B.2.1.4. NCI-supported biospecimen resources should track researchers' requests for specific clinical data to guide the refinement of clinical data collection, as appropriate based on the intended purpose of the resource.

B.2.1.5. NCI-supported biospecimen resources should employ a method for validating the clinical data collected to ensure accuracy in downstream scientific research. The biospecimen resource should develop the validation method or verify that an appropriate validation method is in place.

B.2.1.6. NCI-supported biospecimen resources should comply with applicable privacy statutes and regulations and human subjects protection regulations governing the acquisition of biospecimens and associated clinical data (see Sections C.2, Informed Consent, and C.3, Privacy Protection, for additional information and references). Clinical data associated with the biospecimens only should be used and disclosed for research in compliance, as applicable, with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and with U.S. Department of Health and Human Services (HHS) and FDA human subjects protection regulations.

B.2.2. Longitudinal Clinical Data

B.2.2.1. If the study requirements dictate, NCI-supported biospecimen resources should collect and store longitudinal data following applicable informed consent requirements.

B.2.2.2. Depending on the purpose of the biospecimen resource and/or study design, information linked to biospecimens should include demographic data, lifestyle factors, environmental and occupational exposures, cancer history, structured pathology data, additional diagnostic studies, information on initial staging procedure, treatment data, and any other information relevant to tracking a research participant's future status for clinical outcomes.

B.2.2.3. Databases developed for longitudinal studies should use coded data associated with a biospecimen but maintain a secure link to identifying and contact information to allow additional longitudinal data to be obtained, if permitted by law and by the research participant's consent.

B.2.2.4. NCI-supported biospecimen resources should optimize their policies and protocols to facilitate access to uniform longitudinal data (e.g., treatment and outcome data, as appropriate) and protect research participant privacy and confidentiality.

B.2.2.5. To collect high-quality longitudinal information, NCI-supported biospecimen resources should employ dedicated and trained personnel to curate the longitudinal clinical data validation process and quality assurance/quality control (QA/QC).

B.2.3. Informatics To Support the Tracking of Data

B.2.3.1. A biospecimen resource informatics system should track all aspects of biospecimen collection, processing, and distribution to prevent confusion and to support annotation.

B.2.3.2. A biospecimen resource should comply with applicable human subjects privacy statutes and regulations and local institutional requirements governing the acquisition, storage, and use of biospecimens and associated clinical data (see Sections C.2, Informed Consent, and C.3, Privacy Protection, for further information).

B.3. Quality Assurance/Quality Control

NCI-supported biospecimen resources should develop formalized QA/QC policies to minimize errors that could adversely affect scientific results. QA/QC policies should be customized for the intended and potential uses of biospecimens in a given biospecimen resource.

B.3.1. Quality Management System

Each biospecimen resource should either establish a written QMS or adhere to one published by the organization with which the biospecimen resource is associated. The biospecimen resource's QA/QC programs and approaches for ensuring that program requirements are met should be described in the QMS (ISBER 2005). Procedures for conducting audits in the following areas also should be described in the QMS:

- Equipment maintenance and repair
- Training records and staff adherence to training schedules
- Data management
- Recordkeeping
- Adherence to SOPs

B.3.2. Standard Operating Procedures Manual

Each biospecimen resource should develop an SOPs manual that states policies and describes all procedures in detail.

B.3.2.1. Contents. Specifically, the SOPs manual should include at least the following information:

- Biospecimen handling policies and procedures, including supplies, methods, and equipment used
- Laboratory procedures for tests performed in-house and any division of a biospecimen into aliquots or other processing
- Policies and procedures for shipping and receiving biospecimens, including the material transfer agreements (MTAs) or other appropriate agreements to be used
- Policies for managing records
- Administrative, technical, and physical security
- Information systems security (Stoneburner et al. 2002)

- QA/QC policies and procedures for supplies, equipment, instruments, reagents, labels, and processes employed in sample retrieval and processing
- Safety programs
- Emergency biosafety policies and procedures, including the reporting of staff injury and exposure to potential bloodborne pathogens
- Policies and procedures for the investigation, documentation, and reporting of accidents, errors, and complaints
- Policies and procedures and schedules for equipment inspection, maintenance, repair, and calibration
- Procedures for disposal of medical waste and other biohazardous waste
- Policies and procedures regarding the training of technical and QA/QC staff members
- Procedures for removal of biospecimens from the biospecimen resource
- Policies for the disposition of biospecimens
- Points of contact and designated backup information including names and emergency contact numbers

B.3.2.2. Implementation. The biospecimen resource director and/or the individual responsible for the QA/QC program should review and approve all SOPs and associated process validation studies prior to implementation. Upon implementation, all SOPs should be followed as written.

B.3.2.3. Modifications. Each biospecimen resource should have a document control program and policies for governing, modifying, or revising SOPs. All SOPs should be reviewed at least every 2 years and whenever significant changes in practices, procedures, technology, law, or regulation necessitate an update.

B.3.2.4. Staff access and review. Current copies of the SOPs manual should be stored in designated locations and available to the staff at all times. The staff should review new and revised policies and procedures prior to implementation. Staff review and any associated training should be documented.

B.4. Biosafety

Laboratories and biospecimen resources that handle biospecimens expose their employees to risks involving infectious agents and chemicals as well as the general dangers of a laboratory. A predictable yet small percentage of biospecimens will pose a risk to biospecimen resource personnel who process them. All biospecimens should be treated as biohazards (Grizzle and Fredenburgh 2001). In addition to taking biosafety precautions, biospecimen resources should adhere to key principles of general laboratory safety.

B.4.1. Biohazard Precautions

Laboratories and biospecimen resources should assume that all human specimens are potentially infective and biohazardous (Grizzle and Fredenburgh 2001). OSHA regulations (29 CFR § 1910.1030(f)) require that employers "make available the hepatitis B vaccine and vaccination series to all employees who have occupational exposure, and post-exposure evaluation and follow-up to all employees who have had an exposure incident." Dried blood, tissue, and saliva should be handled according to universal precautions and labeled according to OSHA requirements. Biospecimen resource work practices should be based on universal precautions practices similar to those used in laboratories and clinical settings. Two basic important safety precautions should be followed in laboratories and biospecimen resources that handle biospecimens: (1) Wash

hands frequently and (2) always wear face protection and gloves when handling biospecimens or working within or around freezers. Additional good general laboratory work practices are outlined by Grizzle and Fredenburgh (2001).

A biospecimen resource should establish clear policies regarding the inclusion or exclusion of high-risk biospecimens. For example, depending on the potential for exposure by splash or aerosol, human specimens of unknown infectivity should be handled according to Biosafety Level-2 (BSL-2), as outlined in the Centers for Disease Control and Prevention (CDC)/National Institutes of Health (NIH) booklet "Biosafety in Microbiological and Biomedical Laboratories" (BMBL) (CDC and NIH 1999). According to BSL-2, when biospecimen containers are opened for processing, they should be handled in a BSL-2 biological safety cabinet (hood). All biospecimen resources that handle human specimens should operate under the OSHA bloodborne pathogens standard and should develop an exposure control plan (29 CFR § 1910.1030). Additional precautions apply, as outlined in the BMBL. Some activities may require higher containment, and in other cases, less stringent practices may be acceptable. Therefore, it is best to ensure that biospecimen resource staff members are trained to perform risk assessments and determine appropriate levels of containment.

Biospecimen resources also should establish policies consistent with the NIH Guidelines for Research Involving Recombinant DNA Molecules (http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html) and the CDC's "Additional Requirements for Facilities Transferring or Receiving Select Agents" (42 CFR Part 72).

B.4.2. Biosafety Best Practices

NCI-supported biospecimen resources should:

B.4.2.1. Identify governmental and accrediting agency requirements regarding biohazards and sources of current information concerning laboratory biosafety for use in developing an overall program in safety and associated training programs (see CDC/NIH documents referenced in Section B.4.1, Biohazard Precautions).

B.4.2.2. Identify risks and other general issues of biosafety. Identify frequent biospecimen resource activities, analyze the safety issues involved with each activity, and implement suitable controls.

B.4.2.3. Improve biosafety by developing written working guidelines that are based on Federal and State requirements, experience, and published information. These guidelines should be reviewed and updated regularly and modified in response to problems or if they prove ineffective.

B.4.2.4. Develop and implement a training program. Each employee should receive training in relevant areas of biosafety before beginning work, and the training should be updated annually.

B.4.2.5. Record and arrange for treatment in response to all incidents where personnel are exposed to biohazards or are potentially infected.

B.4.3. General Laboratory Safety

In addition to biosafety, biospecimen resources should follow strict general safety regulations and procedures regarding chemical, electrical, fire, physical, and radiological safety (ISBER 2005; 29 CFR 1910).

B.5. Biospecimen Resource Informatics: Data Management and Inventory Control and Tracking

Driven by the scale of data in genomics and proteomics, informatics systems have become critical to the research enterprise. Informatics systems that support NCI-sponsored biospecimen resources should be robust and reliable to sustain day-to-day operation of a biospecimen resource. Informatics systems should be able to meet changing scientific needs. Interoperability of systems is key to exchanging data and biospecimens.

An informatics system should support all aspects of biospecimen resource operations, including (but not limited to) research participant enrollment and consent; biospecimen collection, processing, storage, and dissemination; QA/QC; collection of research participant data; data security; validation documentation; and management reporting functions. The system also should manage clinical annotations to the biospecimens.

Biospecimen resource informatics systems are a key tool in providing accountability of biospecimens (e.g., location) and related data uses to research participants. All biospecimen resources should implement and operate their informatics systems with security mechanisms such that this demand is met.

B.5.1. Functionality—General

B.5.1.1. At the biospecimen resource level, informatics systems should focus on inventory functions, tracking all phases of biospecimen acquisition, processing, handling, QA/QC, and distribution from collection site (research participant) to utilization (researcher). Restocking of returned, unused samples from the researcher also should be tracked. Tracking should include documenting multiple, preexisting, and/or external physical biospecimen identifiers, such as barcodes with nonidentifying information.

B.5.1.2. The informatics system should have the capability of linking the labels on the physical biospecimen container (e.g., paper labels/barcodes) to other information in the system.

B.5.1.3. Informatics systems should be able to track clinical data associated with a biospecimen and link biospecimen data with external sources of clinical data, where applicable.

B.5.1.4. Tools used to extract structured information from free-text data such as surgical pathology reports should be validated as to their accuracy in performing that task. Biospecimen resources should routinely monitor the performance of such tools.

B.5.1.5. All NCI-supported biospecimen resource databases at an individual institution should be in a secure site monitored by the institution. Plans should be in place for data storage and retrieval in response to a wide variety of conditions that could affect the performance of an informatics system.

Biospecimen resources should eliminate unsecured, ad hoc databases and manage data through the central informatics system. Resources without the capabilities to provide such infrastructure should seek external hosting arrangements for their informatics system.

B.5.1.6. The biospecimen resource informatics system should be capable of monitoring and reporting on biospecimen quality in terms of the scientific best practices described elsewhere in this document.

B.5.1.7. Biospecimen resource informatics systems should be capable of providing vital system statistics and audit logs of all access to protected health information (PHI) in the database.

B.5.2. Functionality—Identification of Biospecimens

B.5.2.1. Each biospecimen should be assigned a unique identifier (or combination of identifiers that makes the biospecimen unique, such as a number and/or barcode). This recommendation is considered most applicable to future biospecimen collections as it would be a laborious task to implement in existing collections. In this context, the scope within which identifiers should be unique applies to an individual system and the biospecimen resources it supports. Mechanisms to address the uniqueness of biospecimen identifiers across biospecimen resources will be addressed as part of the NCI Center for Bioinformatics (NCICB) caBIG™ infrastructure that is under development (see Appendix 1, NCI Infrastructure To Support Informatics Best Practices).

B.5.2.2. The informatics system should be able to track a biospecimen from collection through processing, storage, and distribution as well as associated clinical and epidemiological data.

B.5.2.3. The biospecimen resource database should be updated each time the biospecimen is moved within or out of the biospecimen resource.

B.5.2.4. For informatics purposes, a biospecimen refers to a physically distinct human specimen usually stored in a single container. Multiple physical parts created by extraction, division into aliquots, or other physical division of a biospecimen should be considered new samples, each requiring a new identifier. The origin of each sample should be recorded.

B.5.3. Integration with Local Systems

B.5.3.1. The informatics system at each NCI-supported biospecimen resource should be capable of integrating with the host institution's clinical data systems, including the anatomic pathology laboratory information system, the clinical pathology laboratory information system, and cancer registries. Integration with clinical data systems should conform to HIPAA regulations and human subjects protection regulations, as applicable.

B.5.4. Interoperability

B.5.4.1. Although informatics systems at NCI-supported biospecimen resources will have different informatics requirements based on workflow, systems should be interoperable to integrate clinical and research data and establish distributed biospecimen resources.

B.5.4.2. Informatics systems of NCI-supported biospecimen resources should support a minimum set of common queries that can be submitted to all systems using CDEs. In the future, all NCI-supported systems should support queries across multiple systems or biospecimen resource networks.

See Appendix 1 for a discussion of the NCICB plans to implement caBIG™ and associated tools for enhancing the interoperability of informatics systems at NCI-supported institutions.

B.5.5. Development of Informatics Systems

B.5.5.1. Biospecimen resource informatics management systems should be based on use cases and other techniques (e.g., data or object models) that capture the needs for managing biospecimen resources. SOPs for the activities carried out in a biospecimen resource largely should drive the design of informatics systems.

B.5.5.2. Software and system development methodology should be followed for initial development and subsequent revisions.

B.5.5.3. Software and system engineering organizations are encouraged to meet at least Capability Maturity Model Integration (CMMI) Level 3. Information on CMMI Level 3 is available at http://www.sei.cmu.edu/cmmi/general/general.html)

B.5.6. Ethical and Legal Issues Pertaining to Informatics Systems

B.5.6.1. Permissions and roles should be defined to ensure proper access to data and biospecimens in compliance with all applicable privacy statutes and regulations (i.e., HIPAA) and human subjects regulations (45 CFR Part 46 Subpart A). Data about biospecimens should be provided without reach-through rights to the biospecimen end users' intellectual property (IP) (i.e., consistent with the NIH Principles and Guidelines for Sharing of Biomedical Resources, also known as the NIH Research Tools Policy, available at http://ott.od.nih.gov/policy/research_tool.html and the NIH Data Sharing Policy available at http://grants.nih.gov/grants/policy/data_sharing/). For more information, refer to Section C.5, Intellectual Property and Resource Sharing.

B.5.6.2. NCI-supported biospecimen resources should meet relevant State and Federal requirements that encourage the use of electronic signatures where appropriate and information technology (IT) accessibility standards for handicapped persons.

B.5.6.3. The system should allow biospecimen resource personnel to perform only those operations for which they have permission at the object, record, and attribute levels.

B.5.6.4. An honest broker-guided procedure, if appropriate, should be considered for sharing of samples and data in all NCI-supported biospecimen resources to protect research participants' privacy (Merz et al. 1997). The informatics system and not necessarily an individual can function as the honest broker.

B.5.6.5. If the biospecimen resource is considered a covered entity under HIPAA, compliance with the regulation titled "Security Standards for the Protection of Electronic Protected Health Information," commonly known as the Security Rule, should be achieved to ensure appropriate security of electronic protected health information (see 45 CFR Part 160 and Part 164 Subparts A and C). Detailed information on the HIPAA Security Rule is available at http://www.cms.hhs.gov/EducationMaterials/04_SecurityMaterials.asp.

B.5.6.6. If the creation and operation of the biospecimen resource involves nonexempt human subjects research under HHS human subjects protection regulations, then 45 CFR 46 will apply. Information about the applicability and requirements of 45 CFR Part 46 can be found on the OHRP Web site at http://www.hhs.gov/ohrp/policy/index.html#informed.

B.5.6.7. To determine the appropriate level of security for informatics systems, biospecimen resources are encouraged to refer to National Institute of Standards and Technology Special Publication 800-30 "Risk Management Guide for Information Technology Systems" available at http://csrc.nist.gov/publications/nistpubs/800-30/sp800-30.pdf.

B.5.6.8. NCI-supported biospecimen resources should use or disclose biospecimens consistent with the research participant's permission for the use of his/her biospecimens and develop procedures to identify if and when that research participant has revoked consent for future research use.

C. Ethical, Legal, and Policy Best Practices

In addition to technical considerations relating to the physical quality of a biospecimen, multiple ethical, legal, and policy issues relate to biospecimen collection activities. Key ethical issues include respecting the autonomy of research participants, protecting research participants from breaches of privacy and confidentiality, developing appropriate policies for biospecimen use, and ensuring that biospecimens are used in scientifically sound research. Legal issues include the need for biospecimen resources to adhere to relevant Federal and State regulations surrounding the collection, storage, dissemination, and use of biospecimens.

The ethical, legal, and policy best practices in this document identify key regulations relevant to biospecimen resources and provide additional suggested guidance for NCI-supported biospecimen resources. These best practices are not an exhaustive list of issues and solutions; rather, they are principles to be carefully considered in conjunction with the mission of the biospecimen resource to determine the most appropriate operational policies. The regulations and standards discussed in this document are for research using biospecimens in the United States. Many countries have their own ethical and legal standards for human subjects research including, in some cases, specific provisions for the use of biospecimens. Investigators and biospecimen resources should be aware of foreign standards that may be applicable and address any differences between foreign and U.S. requirements prior to the initiation of a new collaboration or collection.

C.1. Principles for Responsible Custodianship

Responsible custodianship requires careful planning and transparent policies to ensure the long-term physical integrity of the biospecimens while maintaining the privacy and confidentiality of research participants.

C.1.1. NCI-supported biospecimen resources should address formal and continuing responsibility for custodianship of collected biospecimens and associated data as part of the biospecimen resource protocol. Biospecimen resources should address the following questions: (a) How does the biospecimen resource propose to ensure the physical integrity of biospecimens? (b) How does the biospecimen resource propose to ensure the integrity of the research participant data that accompany the biospecimens? (c) What plans and protocols exist for the distribution of samples to investigators? and (d) What are the roles and responsibilities of the biospecimen resource manager and host institution? (Also see Section C.4, Access to Biospecimens and Data.)

C.1.2. Biospecimen resources should address the handling and disposition of biospecimens and associated data at one or more of the following points: (a) End of the budget period of the grant, (b) accomplishment of the specific research objectives of the study, (c) depletion of biospecimens, (d) achievement of critical data endpoints, or (e) research participant request for discontinuation of participation. (Also see Section C.2, Informed Consent.)

C.1.3. NCI-supported biospecimen resources should establish and document transparent policies governing the retention of biospecimens, data, and records pertaining to informed consent and the identity of research participants. In addition, usage agreements, such as MTAs, should specify the retention policy of the recipient investigator.

- The retention of clinical biospecimens is governed by Federal and/or State laws related to the retention of medical records.
- For research biospecimens, permanent storage generally is preferred, subject to sufficient resources and storage space and foreseeable research utility (i.e., QA/QC, dated datasets).
- Biospecimen resources should be reviewed periodically (e.g., at the time of funding renewal) to determine the utility of existing biospecimens, the need for new biospecimens, etc.
- In the event that biospecimen resources close because of lack of funding or otherwise cannot maintain or use the biospecimens, the availability of the biospecimens for transfer, if permitted, should be announced to the research community by means appropriate for reaching a wide audience. The transfer of such biospecimens must be consistent with human subjects regulations.

C.1.4. One aspect of responsible custodianship is the appropriate management of conflicts of interest. Biospecimen resources should adhere to regulations regarding conflict of interest at 42 CFR Part 50 Subpart F, as well as other applicable regulations.

C.1.5. Biospecimen resources should have transparent policies for maintaining the privacy and security of the biospecimens and associated clinical data, if applicable. Specifically, biospecimen resources that store coded samples and data should have policies regarding how the link or code that allows identification of research participants will be maintained.

C.2. Informed Consent

Informed consent (pursuant to the human subjects regulations at 45 CFR Part 46 Subpart A) is designed to present potential human subjects with sufficient information—including anticipated procedures, risks, and benefits—to make an informed decision to participate in research studies. Obtaining informed consent for the collection and storage of biospecimens and for their use in future research is challenging since the specifics of the future research often are not known at the time of biospecimen collection. Despite this challenge, the informed consent information describing the nature and purposes of the research should be as specific as possible. The specific type of research that will be conducted in the future on contributed biospecimens may be sufficiently anticipated and described in the original informed consent to satisfy HHS regulations. In addition, under HHS regulations at 45 CFR Part 46 Subpart A, informed consent may not be required even if the research is considered human subjects research if (1) the human subjects research is exempt from the regulations at 45 CFR § 46.101(b), or (2) the research is nonexempt human subjects research that has been granted an informed consent waiver by an institutional review board (IRB) under 45 CFR § 46.116(c) or (d). See the OHRP guidance document at http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm for more information.

C.2.1. Federal Regulations and Guidelines Pertaining to Informed Consent

C.2.1.1. HHS-conducted or -supported research on human subjects is primarily regulated by 45 CFR Part 46. The HHS regulations describe both when informed consent is required and what elements must be in an informed consent document. As custodians of human specimens, biospecimen resources should track whether appropriate informed consent is present (if applicable) or the reason why informed consent is not necessary. See the OHRP Web site for

guidance on when informed consent is required and the necessary elements of informed consent (http://www.hhs.gov/ohrp/policy/index.html#informed).

C.2.1.2. The OHRP has issued guidance on regulatory requirements that must be satisfied by biospecimen resources (available at http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm and http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm). The OHRP recommends that the following should be included in informed consent documents for biospecimen collection:

- A clear description of the operation of the biospecimen resource. This description could include details that might be of interest to human subjects, such as whether identifiable information will be maintained in the biospecimen resource and/or whether research results will be linked to the biospecimen.
- The conditions under which data and samples will be released to recipient-investigators. See Section C.4, Access to Biospecimens and Data, for NCI recommendations.
- Procedures for protecting the privacy of human subjects and confidentiality of data. See Section C.3, Privacy Protection, for NCI recommendations.
- Specific descriptions of the nature and purpose of the research.
- Where human genetic research is anticipated, information about the consequences of DNA typing.

C.2.1.3. FDA regulations regarding informed consent should be considered when human specimens are used for clinical research (see 21 CFR Parts 812 and 21 CFR Parts 50 and 56).

C.2.2. Additional NCI Recommendations Pertaining to Informed Consent

C.2.2.1. The NCI recommends informed consent whenever possible, consistent with applicable regulations. Respect for individuals who have provided data or biospecimens for research should be of paramount concern, and their preferences should be considered when deciding whether informed consent should be sought. Some individuals may prefer use of unidentified samples or waiver of consent to being recontacted to obtain consent for additional research or future uses.

C.2.2.2. For biospecimens collected during the course of medical care, the timing of consent (e.g., before or after a medical procedure) to use biospecimens for research purposes should not be imposed rigidly but instead should be informed by a number of important considerations, including ethical guidelines and logistical constraints.

Generally, consent should be obtained prior to the medical procedure, but post–medical procedure consent may be appropriate in some circumstances. These decisions should be made on a case-by-case basis with sensitivity to the situation a patient faces when undergoing a medical procedure or a test for a serious disease. For example, post–medical procedure consent may be acceptable for the use of remnant human specimen beyond what is needed for diagnostic purposes if it was not possible to previously consent the patient due to considerations about illness, undue stress, or the ability of the patient to fully comprehend what is being asked. However, in all cases where biospecimens are collected from the individual for research purposes or the procedure for

collecting a biospecimen for clinical purposes is changed to meet a research need, informed consent must be obtained prior to the collection of the biospecimen.

C.2.2.3. The informed consent documents used by NCI-supported biospecimen resources should employ clear and specific language to address the use of biospecimens and/or data by private or for-profit entities and the possibility of research leading to future development of commercial products, as appropriate.

C.2.2.4. The informed consent document should state whether or not individual or aggregate research results will be released to the human subject, the subject's health care provider, or the subject's family.

C.2.2.5. The informed consent document should describe how human subject data will be used and stored. Where applicable, the informed consent document should state whether identifiable or coded information will be maintained in the biospecimen resource and if research results will be linked to other data about the human subject, such as clinical data obtained from anatomic pathology and clinical pathology laboratory information systems and cancer registries. (Refer to B.5.3.1. for further recommendations on the integration of informatics systems.) If longitudinal data will be collected, the informed consent document should state that the subject's medical records will be accessed for this purpose. Informed consent documents also should describe whether the biospecimens and/or the data associated with or derived from biospecimens will be shared with other investigators and, if so, the oversight mechanisms for such sharing.

C.2.2.6. If a study includes genetic sequencing or analysis, the informed consent document should include information about the potential risks to the subject posed by such research. While the frequency of harm is not known, possible consequences could include paternity determinations or potential employment or insurance discrimination if the research reveals the individual to be at increased risk for certain diseases. In the case of genetic analyses, such risks also could pertain to the subject's family members.

C.2.2.7. If appropriate to the study design or the biospecimen resource's mission, human subjects may be allowed to specify the types of research for which the contributed biospecimens will be used via a tiered system of consent.

Examples:

- My tissue may be kept for use in research to learn about, prevent, or treat cancer.
- My tissue may be kept for use in research to learn about, prevent, or treat other health problems (e.g., diabetes, Alzheimer's disease, or heart disease).

While a tiered system of consent will provide the human subject with greater specificity about future research, it also could lead to ambiguities in terms of how to classify certain types of inter- or multidisciplinary research. Tiered consent also may be inappropriate if the purpose of the biospecimen resource is to provide biospecimens for a very broad range of research, in which case providing human subjects with a list of potential types of research would be burdensome and uninformative. Tiered consent only should be used if a sophisticated system capable of tracking the levels of consent for each human

subject already is in place. The logistics of monitoring the various levels of consent in a tiered system are complex and should be attempted only if the biospecimen resource has experience with a suitable tracking system.

C.2.2.8. If appropriate, informed consent documents may provide an option for human subjects to select whether they would be willing to be recontacted about the use of their biospecimens and/or data in future research studies.

C.2.2.9. NCI-supported biospecimen resources should develop policies and procedures to track records for human subjects who discontinue participation. Informed consent documents should highlight the human subject's ability to discontinue participation and describe what will take place should this occur.

- In the event that participation in the research study is discontinued, any remaining identifiable biospecimens and associated clinical data must be withdrawn from the biospecimen resource. However, samples and/or clinical data that have been transferred from the biospecimen resource to investigators and research data already generated from samples need not be withdrawn. Instead, if a biospecimen resource learns about the discontinuation of participation of a human subject, the NCI considers the biospecimen resource ethically obligated to inform investigators who received specimens derived from that individual.
- If an investigator receives individually identifiable biospecimens from a biospecimen resource, the investigator would be conducting human subjects research under 45 CFR Part 46, and if a human subject discontinues participation, the investigator would be required to withdraw that subject from the research study.
- Specific actions that a biospecimen resource or recipient investigators, as appropriate, could take if a human subject discontinues participation are as follows: (1) Cease using the human subject's individually identifiable specimens and private information in the study; (2) remove the human subject's individually identifiable information from the biospecimens and eliminate private information (if doing so would render the specimen not individually identifiable to the investigators), or (3) destroy the human subject's individually identifiable specimen and private information.
- If participation is discontinued, biospecimen resource managers should be sensitive to cultural issues and should work with affected groups to develop mechanisms for the proper destruction of biospecimens or, if needed, returning biospecimens to the individual or affected group, as appropriate.

C.2.2.10. Studies that use identifiable biospecimens and/or data from children that are obtained with parental or guardian permission should consider the need for obtaining informed consent when a child reaches the legal age to consent for a research study. Such reconsent issues may best be addressed by IRBs at the time the board reviews the initial protocol.

C.2.2.11. NCI-supported biospecimen resources should establish and document transparent policies governing the retention of biospecimens and records pertaining to informed consent and the identity of human subjects. These policies should be provided to subjects, either in the informed consent document or in supporting information. (Also see Section C.1, Principles for Responsible Custodianship.)

For additional information about IRBs and the requirement for OHRP-approved assurance of compliance, see the OHRP Web site at http://www.hhs.gov/ohrp/.

C.3. Privacy Protection

Research depends on protecting the privacy of individuals who contribute biospecimens to biospecimen resources and on maintaining the confidentiality of associated clinical data and information (Eiseman et al. 2003). Applying the highest possible ethical standards is necessary to ensure the support and participation of research participants, physicians, researchers, and others in biospecimen resource activities (Friede et al. 2003). With the recent advances in genomic and proteomic technology, the sequencing of the human genome, and the increasing reliance of biospecimen resources on electronic and Web-based databases for data tracking, it is even more crucial to address the risk of breaches in privacy. The unintended release or disclosure of sensitive information can place individuals at risk for discrimination and related groups at risk for stigmatization, although the frequency of these types of harms is unknown.

C.3.1. Federal Regulations Pertaining to Privacy

The HHS-issued regulation titled "Standards for Privacy of Individually Identifiable Health Information," commonly known as the HIPAA Privacy Rule (see 45 CFR Part 160 and Subparts A and E of Part 164), was created to protect the privacy of health information that identifies an individual while still allowing other activities of benefit to society, such as research. While the Privacy Rule does not apply to biospecimens directly, it may affect some biospecimen resources in that human specimens often are accompanied by identifiable health information that is necessary for tracking or longitudinal research. When determining if the Privacy Rule applies to an individual biospecimen resource and its research activities, the following points must be considered:

- Covered entities. The Privacy Rule regulates the use and disclosure of PHI by covered entities. Under the Privacy Rule, a covered entity is defined as "a health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard" (Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, available at: http://privacyruleandresearch.nih.gov/pr_02.asp).

  In general, a biospecimen resource is not considered a covered entity "unless the organization maintaining the tissue repository conducts some other activity that makes it a covered entity. For example, tissue repositories that conduct testing of specimens for the benefit of transplant recipients based on another health care provider's orders would be covered providers under HIPAA if they conduct electronic transactions for which the HHS has adopted standards" (Research Repositories, Databases, and the HIPAA Privacy Rule, available at: http://privacyruleandresearch.nih.gov/research_repositories.asp). Even if a biospecimen resource is not a covered entity, it still is important to understand what constitutes PHI and the conditions under which it can be released by a covered entity, as these factors may affect what types of data will accompany a biospecimen and therefore what types of studies may be conducted using the biospecimen.

- Protected health information. The Privacy Rule applies to PHI, defined as "individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. Protected health information excludes education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records

described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer" (45 CFR § 160.103). As stated in 45 CFR § 164.502, "Health information that meets the standard and implementation specifications for de-identification under §164.514(a) and (b) is considered not to be individually identifiable health information."

- Privacy Rule Authorization. "A valid Privacy Rule Authorization is an individual's signed permission that allows a covered entity to use or disclose the individual's PHI for the purposes, and to the recipient or recipients, as stated in the Authorization. When an Authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as a specific research activity, but the subsequent use or disclosure by a covered entity of information from the database for a specific research study will require separate Authorization unless the PHI use or disclosure is permitted without Authorization…. An Authorization differs from an informed consent in that an Authorization focuses on privacy risks and states how, why, and to whom the PHI will be used and/or disclosed for research. An informed consent, on the other hand, provides research subjects with a description of the study and of its anticipated risks and/or benefits, and a description of how the confidentiality of records will be protected, among other things. An Authorization can be combined with an informed consent document or other permission to participate in research" (Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, available at: http://privacyruleandresearch.nih.gov/pr_02.asp).

For detailed information on the HIPAA Privacy Rule, see the following Web pages:

- http://privacyruleandresearch.nih.gov/
- http://www.hhs.gov/ocr/hipaa/

C.3.2. Additional NCI Recommendations Pertaining to Privacy

C.3.2.1. NCI-supported biospecimen resources should establish clear policies for protecting the privacy of identifiable information. These policies may include data encryption, coding, establishing limited access or varying levels of access to data by biospecimen resource employees, use of nondisclosure agreements, and use of an honest broker system. For more information on honest broker systems, see Section B.5, Biospecimen Resource Informatics.

C.3.2.2. Biospecimen resources may consider using certificates of confidentiality to protect identifiable research information from forced disclosure. Under section 301(d) of the Public Health Services Act (42 United States Code 241(d)), the NIH may issue certificates of confidentiality to authorize persons engaged in biomedical, behavioral, clinical, or other research to refuse to disclose identifying information about research participants in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. Certificates of confidentiality should be considered by the biospecimen resource and/or the recipient investigator depending on the level of privacy protection indicated by the study design. Certificates of confidentiality may not be appropriate for all biospecimen resources. If a certificate of confidentiality is obtained, this should be explicitly stated in the informed consent document.

Further information about certificates of confidentiality may be found at http://grants2.nih.gov/grants/policy/coc/index.htm.

C.3.2.3. In applications for support, biospecimen resources should document their policies for maintaining the privacy of research participants, including descriptions of mechanisms for auditing effectiveness, enforcement measures, and required training for employee, and specify security measures pertaining to employee access to data and biospecimens. The level of security should be appropriate to the type of biospecimen resource and the sensitivity of the data it houses.

C.3.2.4. NCI-supported biospecimen resources also should ensure compliance with all applicable State and local statutes and regulations pertaining to privacy.

C.4. Access to Biospecimens and Data

Access to human specimens and data for research purposes is crucial for fields such as genomics, proteomics, metabolomics, molecular imaging, and nanotechnology. Researchers in these areas often rely on federally funded biospecimen resources for high-quality biospecimens and associated data. To best serve the needs of the research community, NCI-funded biospecimen resources should establish guidelines for sample distribution (and clinical data sharing) consistent with ethical principles, governing statutes and regulations, and, if applicable, informed consent language. These guidelines should be:

- Clear to ensure their comprehension and adoption;
- Flexible so that biospecimen resources may be responsive to changing scientific needs;
- Amendable to facilitate their adaptability over time; and
- General enough so they may be applied to different kinds of biospecimen resources.

In addition, the guidelines should delineate when biospecimens (and clinical data) are narrowly or broadly accessible and what justifications for the biospecimen request are expected by funded biospecimen resources. Guidelines should apply to all new collections and, whenever possible, to existing collections.

C.4.1. Access decisions should be guided by a set of general principles that include:

- Timely, equitable, and appropriate access to human specimens without undue administrative burden
- Fair and clearly communicated access procedures
- Local principles and ethical considerations as primary factors
- Scientific merit with institutional research qualifications, proven investigator experience with the proposed method, and a research plan appropriate to answer the study question
- Appropriate assignment of resources based on the nature of the scientific investigation (e.g., discovery, prevalence, initial validation, hypothesis testing) and the need for annotation. The level of identifiability of the biospecimen and related transfer documents should be appropriate for the proposed research.
- An appeals process for addressing disputes over allocation decisions
- An investigator agreement covering confidentiality, use, disposition, and security of biospecimens and associated data
- The parties' written agreement in an MTA or other appropriate document that is consistent with the NIH Research Tools Policy (http://ott.od.nih.gov/policy/research_tool.html)

C.4.2. A scientifically sound and appropriate research plan is needed to justify access requests. If applicable to the study design and biospecimen resource purpose, the following specific issues should factor in access decisions:

- Use of standardized, validated research biomarker assay methodology
- Statistical evaluation that shows that the study question can be addressed with the samples available and a negotiated arrangement with a clinical protocol coordinating group to provide timely statistical analysis of study results
- Compliance with protocol-specific requirements needed to achieve study goals before other access is considered
- Confirmation that an investigator has defined funding and IRB approval for the project, if applicable (for information on application, exemption from, or waiver of IRB approval, see HHS human subjects guidance at http://www.hhs.gov/ohrp/policy/index.html#human)
- Agreement that the investigator will publish or provide information about the project outcome according to rules agreed upon by the biospecimen resource and the investigator and according to NIH policies, including the Research Tools Policy available at http://ott.od.nih.gov/policy/research_tool.html. Of note, the NIH Research Tools Policy permits reasonable short-term publication delays (e.g., to file a patent or allow a collaborator to review a manuscript).

C.4.3. Appropriate policies should be developed to ensure that researcher access to biospecimens and associated clinical data is appropriate and in compliance with all applicable Federal and State privacy statutes and regulations and human subjects regulations. The following should be considered:

- Inclusion of appropriate provisions for the protection of the confidentiality and security of biospecimens and associated data in the usage agreement between the biospecimen resource and the researcher. For OHRP guidance on the use of coded biospecimens and data, see http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm.
- Consistency of the MTA or other appropriate document with the NIH Research Tools Policy (http://ott.od.nih.gov/policy/research_tool.html)

C.4.4. If necessitated by data type and sensitivity, NCI-supported biospecimen resources should use a system of data access with defined levels of access privileges for biospecimen resource staff.

C.4.4.1. Access levels should be described in the protocol for operation of the biospecimen resource and should be approved by an IRB and/or bioethics/scientific advisory board, as appropriate.

C.4.4.2. Access to research participants' identities and medical, genetic, social, and personal histories should be restricted to only those biospecimen resource staff members who need to access such records as part of their assigned duty or to those persons permitted access by law.

C.4.4.3. The number of personnel allowed to access links and re-identify information should be kept to a minimum, and access should be appropriately monitored to ensure compliance.

C.4.5. Charges for samples, if any, should be used only to recover reasonable costs associated with operation of the biospecimen resource.

C.5. Intellectual Property and Resource Sharing

Inventions and data arising from research using annotated biospecimens may have commercial value. As researchers and industry sponsors have sharply increased their demand for properly prepared and clinically annotated biospecimens, some institutions have begun to assert control over biospecimens, associated data, and research findings. The current variability in IP policies at institutions hosting NCI-supported research and biospecimen resources may ultimately lead to problems in biospecimen and data access, timely and open publication, sharing of research findings, and establishment of new biospecimen resources. Sharing of research data obtained through use of biospecimens and associated research materials (e.g., derivatives) is essential for the advancement of science. Accordingly, research data and tools generated through use of biospecimens should be shared in a timely manner consistent with the NIH Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/) and the NIH Research Tools Policy (http://ott.od.nih.gov/policy/research_tool.html).

C.5.1. For the transfer of materials in academic-industrial collaborations, the NIH Simple Letter of Agreement (SLA), the Uniform Biological Material Transfer Agreement (UBMTA), or other agreement with terms consistent with the NIH Research Tools Policy and the NIH Data Sharing Policy should be used. Clinical protocols are not designed to document material transfers, and they are usually inappropriate for this purpose. The above agreements should be modified where necessary to cover human subjects research. Desirable terms in an MTA include:

- Clear descriptions of the biospecimens and identification of the institutions involved
- Clear identification of human subjects status of the biospecimens and associated obligations
- Acknowledgement of the recipient's right, or lack thereof, to further distribute the biospecimens
- Assurances of the end user's academic freedom and the right to publish research results
- IP terms consistent with the NIH Research Tools Policy (see http://ott.od.nih.gov/policy/research_tool.html) such as no reach-through to end-users' intellectual property and the sharing of research resources and data with the research community

For reference, Appendix 2 contains a sample MTA addressing the transfer of human unidentifiable or coded biospecimens.

The following Internet sites are relevant to this issue:

- http://ott.od.nih.gov/policy/research_tool.html
- http://www.autm.net/aboutTT/aboutTT_umbta.cfm
- http://grants.nih.gov/grants/policy/data_sharing/

C.5.2. Biospecimen resource staff, as custodians of biospecimens, are not considered a priori inventors under patent law for inventions made using materials distributed by the biospecimen resource. In general, staff should be informed that one whose sole contribution to an invention consists of the routine collection, handling, storage, and disbursement of biospecimens might not rise to the level of "inventor." Inventorship is determined by patent law and should be considered on a case-by-case basis by trained legal personnel.

C.5.3. Biospecimen resources have no inherent rights to future IP, such as reach-through rights in inventions made by investigators using samples obtained from the biospecimen resource.

C.5.4. Through MTAs or other appropriate documents, research data and research resources obtained using biospecimens should be made available to the research community, consistent with the NIH Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/) and the NIH Research Tool Policy (http://ott.od.nih.gov/policy/research_tool.html).

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Merz J.F, Sankar P, Taube SE, LiVolsi VA. Use of Human Tissues in Research: Clarifying Clinician and Researcher Roles and Information Flows. Journal of Investigative Medicine. 1997:45:252-257.

Stoneburner G, Goguen A, Feringa A. Risk Management Guide for Information Technology Systems [online]. Gaithersburg, MD: National Institute of Standards and Technology; 2002. Available at http://csrc.nist.gov/publications/nistpubs/800-30/sp800-30.pdf. Accessed February 28, 2007.

WEB RESOURCES[6]

Biospecimen Research Network

Biospecimen Research Network
Office of Biorepositories and Biospecimen Research
National Cancer Institute
http://biospecimens.cancer.gov/sciences/symposium.asp

Code of Federal Regulations

Government Printing Office Access
http://www.gpoaccess.gov/cfr/index.html

Electronic Records and Electronic Signatures

Electronic Records; Electronic Signatures
Office of Regulatory Affairs, U.S. Food and Drug Administration
http://www.fda.gov/ora/compliance_ref/part11/

Health Information Portability and Accountability Act (HIPAA) of 1996

HIPAA Privacy Rule Information for Researchers
National Institutes of Health
http://privacyruleandresearch.nih.gov/

HIPAA Security Rule Information Series
Centers for Medicare and Medicaid Services
Department of Health and Human Services
http://www.cms.hhs.gov/EducationMaterials/04_SecurityMaterials.asp

Research Repositories, Databases, and the HIPAA Privacy Rule
National Institutes of Health
http://privacyruleandresearch.nih.gov/research_repositories.asp

Medical Privacy – National Standards to Protect the Privacy of Personal Health Information
Office for Civil Rights – HIPAA
Office for Civil Rights
Department of Health and Human Services
http://www.hhs.gov/ocr/hipaa/

Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule
National Institutes of Health
http://privacyruleandresearch.nih.gov/pr_02.asp

[6] All Web sites listed above were accessed on February 28, 2007.

Human Subjects Protections

Office for Human Research Protections
Department of Health and Human Services
http://www.hhs.gov/ohrp/

Human Subjects Policy Guidance
Office for Human Research Protections
Department of Health and Human Services
http://www.hhs.gov/ohrp/policy/index.html#human

Guidance on Research Involving Coded Private Information or Biological Specimens
Office for Human Research Protections
Department of Health and Human Services
http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm

Informed Consent Policy Guidance
Office for Human Research Protections
Department of Health and Human Services
http://www.hhs.gov/ohrp/policy/index.html#informed.

Issues to Consider in the Research Use of Stored Data or Tissues
Office for Human Research Protections
Department of Health and Human Services
http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm

Informatics System Development

Capability Maturity Model Integration
Carnegie Mellon® Software Engineering Institute
http://www.sei.cmu.edu/cmmi/

Informatics System Security

Risk Management Guide for Information Technology Systems
National Institute of Standards and Technology
http://csrc.nist.gov/publications/nistpubs/800-30/sp800-30.pdf

National Institutes of Health Policies and Guidelines

Certificates of Confidentiality Kiosk
Office of Extramural Research
National Institutes of Health
http://grants2.nih.gov/grants/policy/coc/index.htm

Guidelines for Research Involving Recombinant DNA Molecules
Office of Biotechnology Activities
National Institutes of Health
http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

NIH Data Sharing Policy
Office of Extramural Research
National Institutes of Health
http://grants.nih.gov/grants/policy/data_sharing/

NIH Research Tools Policy
Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts
Office of Technology Transfer
National Institutes of Health
http://ott.od.nih.gov/policy/research_tool.html.

Uniform Biological Material Transfer Agreement (UBMTA)

UBMTA Federal Register
The Association of University Technology Managers
http://www.autm.net/aboutTT/aboutTT_umbta.cfm

GLOSSARY OF TERMS

This glossary is included to provide instruction as to how terms used in the NCI Best Practices for Biospecimen Resources should be interpreted. Wherever possible, standardized definitions from Federal documents and/or the NCI Thesaurus[7] were used. Where such sources were not available or appropriate, definitions were selected from widely used texts, such as Black's Law Dictionary (8th ed.), Taber's Cyclopedic Medical Dictionary (20th ed.), Merriam-Webster Dictionary [online]; reports specific to biospecimen resources, such as ISBER "Best Practices for Repositories I" (2005), and RAND Corporation's "Case Studies of Existing Human Tissue Repositories" (2003) or relevant Web sites such as the OSHA Web site. The citation "NCI Best Practices working definition" refers to definitions drafted specifically for this document by the NCI in consultation with appropriate experts. In some cases, two definitions may be listed for a single term to convey both a general and a biospecimen resource–specific meaning or to provide definitions from two Federal regulations. Where two definitions are listed, the first definition contains the meaning most relevant to the NCI Best Practices.

Accident. An unforeseen and unplanned event or circumstance frequently causing loss or injury (NCI Thesaurus).

Aerosol. A fine mist or spray which contains minute particles (Centers for Disease Control and Prevention Special Pathogens Branch, Glossary of Terms, http://www.cdc.gov/ncidod/dvrd/spb/mnpages/glossary.htm).

Aliquot. Pertaining to a portion of the whole; any one of two or more samples of something, of the same volume or weight (NCI Thesaurus).

Analyte. The sample being analyzed (NCI Best Practices working definition).

Annotation. Explanatory or additional information associated with a particular biospecimen. Annotations may be added by either the pathologist or the resource collector (NCI Best Practices working definition).

Associated data. See Biospecimen associated data.

Audit. 1. A documented review of procedures, records, personnel functions, equipment materials, facilities, and/or vendors to evaluate adherence to written standard operating procedures or government laws and regulations (ISBER 2005). **2.** To perform an audit (Merriam-Webster Dictionary).

Best practices. Standard operating procedures that are considered state-of-the-science consistent with all applicable ethical, legal, and policy statutes, regulations, and guidelines (NCI Best Practices working definition).

Biohazard. A combination of the words biological hazard. Organisms or products of organisms that present a risk to humans (Occupational Safety and Health Administration, http://www.osha.gov/doc/outreachtraining/htmlfiles/hazglos.html).

Biorepository. An organization, place, room, or container (a physical entity) where biospecimens are stored. In the context of the NCI Best Practices, only biorepositories containing human specimens collected with an intention to use them for research purposes (research biorepositories) are addressed. The physical structure, policies, and the biospecimens and data contained within it are defined collectively as a biospecimen resource, defined below (NCI Best Practices working definition).

[7] A collaborative effort of the NCI Office of Communications and the NCICB to standardize terminology within the NCI, available at http://nciterms.nci.nih.gov/NCIBrowser/Dictionary.do.

Biosafety. Biological safety, or biosafety, is the application of knowledge, techniques, and equipment to prevent personal, laboratory, and environmental exposure to potentially infectious agents or biohazards. Biosafety defines the containment conditions under which infectious agents can be safely manipulated. The objective of containment is to confine biohazards and to reduce the potential exposure of the laboratory worker, persons outside of the laboratory, and the environment to potentially infectious agents (U.S. Environmental Protection Agency, Terminology Reference System, http://oaspub.epa.gov/trs/trs_proc_qry.navigate_term?p_term_id=1317&p_term_cd=TERM).

Biosafety level. Specific combinations of work practices, safety equipment, and facilities, which are designed to minimize the exposure of workers and the environment to infectious agents. Biosafety level 1 (BSL-1) applies to agents that do not ordinarily cause human disease. Biosafety level 2 (BSL-2) is appropriate for agents that can cause human disease, but whose potential for transmission is limited. Biosafety level 3 (BSL-3) applies to agents that may be transmitted by the respiratory route which can cause serious infection. Biosafety level 4 (BSL-4) is used for the diagnosis of exotic agents that pose a high risk of life-threatening disease, which may be transmitted by the aerosol route and for which there is no vaccine or therapy (Centers for Disease Control and Prevention Special Pathogens Branch, Glossary of Terms, http://www.cdc.gov/ncidod/dvrd/spb/mnpages/glossary.htm).

Biospecimen. A quantity of tissue, blood, urine, or other human-derived material. A single biopsy may generate several biospecimens, including multiple paraffin blocks or frozen biospecimens. A biospecimen can include subcellular structures (DNA), cells, tissue (bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, and placenta). Portions or aliquots of a biospecimen are referred to as samples (NCI Best Practices working definition).

Biospecimen-associated data. Any data associated and collected with a biospecimen, including research data, phenotypic data, clinical data, epidemiologic data, and biospecimen resource data (NCI Best Practices working definition).

Biospecimen resource. A collection of human specimens and associated data for research purposes, the physical entity where the collection is stored, and all relevant processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer (NCI Best Practices working definition).

Biospecimen resource informatics system. The software, hardware, written documents, support, operating procedures, and training necessary to annotate, track, and distribute biospecimens within a biospecimen resource or resources (NCI Best Practices working definition).

Bloodborne pathogen. Pathogenic microorganisms that are present in human blood and can cause disease in humans. These pathogens include, but are not limited to, hepatitis B virus and human immunodeficiency virus (Occupational Safety and Health Administration Bloodborne Pathogen Standards, 29 CFR § 1910.1030).

caBIG™ (cancer Biomedical Informatics Grid). A voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools, creating a world wide web of cancer research. The goal is to speed the delivery of innovative approaches for the prevention and treatment of cancer. The infrastructure and tools created by caBIG™ also have broad utility outside the cancer community. caBIG™ is being developed under the leadership of the National Cancer Institute's Center for Bioinformatics (NCI Thesaurus). For more information, visit https://cabig.nci.nih.gov.

caBIG™ (cancer Biomedical Informatics Grid) compatibility. Refers to meeting caBIG™ requirements. To aid in the creation of software that will be able to interoperate within the caBIG™ program, a set of compatibility guidelines was developed that spells out requirements for interoperability in areas of Interface Integration, Vocabularies/Terminologies and Ontologies, Information Models and

Data Elements. Systems that meet the requirements are said to be "caBIG™ compatible" (caBIG™ Glossary, https://cabig.nci.nih.gov/overview/Glossary).

caDSR (cancer Data Standards Repository). The standards repository that hosts common data elements and information models developed by various NCI-sponsored organizations. caDSR tools facilitate the search and retrieval of common data elements and models. caDSR is the single, authoritative source of common data (NCI Best Practices working definition). For more information, visit http://ncicb.nci.nih.gov/NCICB/infrastructure/cacore_overview/cadsr.

Capability Maturity Model Integration (CMMI). A process improvement approach that provides organizations with the essential elements of effective processes. It can be used to guide process improvement across a project, a division, or an entire organization. CMMI helps integrate traditionally separate organizational functions, set process improvement goals and priorities, provide guidance for quality processes, and provide a point of reference for appraising current processes (Carnegie Mellon® Software Engineering Institute CMMI Web site, http://www.sei.cmu.edu/cmmi/cmmi.html).

caTIES (cancer Text Information Extraction System). An application for extracting free-form text, codes, and other information from pathology reports to populate caBIG™-compliant data structures, which provide researchers with the ability to query, browse, and acquire annotated biospecimen data and physical material across a network of federated sources (NCI Best Practices working definition).

caTISSUE Core. A Web-interfaced biospecimen inventory and tracking application that will encompass a core database module for those biospecimen resources in need of new solutions, as well as application programming interfaces, software development toolkits, and additional annotation modules for those biospecimen resources with preexisting systems that wish to link into the virtual tissue repositories and query across biospecimen resources (NCI Best Practices working definition).

Clinical data. 1. Factual information (as measurements or statistics) or observations used as a basis for reasoning, discussion, or calculation pertaining to clinical trials, diagnosis, or treatment (NCI Best Practices working definition). **2.** Data obtained through patient examination or treatment (NCI Thesaurus).

Clinical research. Research conducted with human subjects or on material of human origin in which an investigator directly interacts with human subjects; includes development of new technologies, mechanism of human diseases, therapy, clinical trials, epidemiology, behavior and health services research (NCI Thesaurus).

Code of Federal Regulations (CFR). The annual collection of executive-agency regulations published in the daily Federal Register, combined with previously issued regulations that are still in effect (Black's Law Dictionary). See http://www.gpoaccess.gov/cfr/index.html for more information.

Coded. Having (1) identifying information (such as name or Social Security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code, enabling linkage of the identifying information to the private information or specimens (Office for Human Research Protections, Guidance on Research Involving Coded Private Information or Biological Specimens, http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm)

Collection. 1. The act of gathering things together; having been brought together in one place (NCI Thesaurus). Also see Retrieval. **2.** An accumulation of objects gathered for study, comparison, or exhibition (Merriam-Webster Dictionary).

Common Data Elements (CDEs). 1. A CDE identifies a piece of data that may be recorded in a system. A CDE is described by metadata such as its name, definition, unit of measurement, data type (e.g., character, numeric, date) and the allowed values it may take. CDEs become "common" by making

these metadata available in a suitable repository such that they can be used by multiple systems and users. The caDSR used by caBIG™ is such a repository and is based on the ISO/IEC 11179 standard. This standard provides a specific technical description of a CDE (NCI Best Practices working definition). **2.** Data elements that have been determined to be identical between projects or contexts (NCI Thesaurus).

Confidentiality. 1. Secrecy; the state of having the dissemination of certain information restricted (Black's Law Dictionary). **2.** The ethical principle or legal right that a physician or other health professional will hold secret all information relating to a patient, unless the patient gives consent permitting disclosure (NCI Thesaurus).

Conflict of interest. Exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the Public Health Service–funded research. Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to: (1) Public disclosure of significant financial interests; (2) Monitoring of research by independent reviewers; (3) Modification of the research plan; (4) Disqualification from participation in all or a portion of the research funded by the Public Health Service; (5) Divestiture of significant financial interests; or (6) Severance of relationships that create actual or potential conflicts (42 CFR § 50.605)

Container. 1. A compartment or receptacle (e.g., box, jar, cooler, package enclosure) for holding one unit or units of biospecimen(s), which may be used to transport or ship a biospecimen in a safe and convenient manner (NCI Best Practices working definition). **2.** An object that can be used to hold things (NCI Thesaurus).

Covered entity. A health plan, a health care clearinghouse or a health care provider who transmits any health information in electronic form in connection with a transaction covered by this subchapter (45 CFR § 160.103).

Custodianship. The caretaking responsibility for a biospecimen collection, including management and documentation, as well as rights to determine the conditions under which biospecimens are accessed and used (NCI Best Practices working definition).

Data. 1. Factual information (e.g., measurement, statistic, numerical value) derived from scientific experiments or diagnostic procedures organized especially for scientific analysis in a numerical form suitable for digital transmission or processing by computer, digitally transmitted or processed and used as a basis for reasoning, discussion, or calculation. The information may include both useful and irrelevant or redundant information that must be processed to be meaningful (NCI Best Practices working definition). **2.** A collection or single item of factual information, derived from measurement or research, from which conclusions may be drawn (NCI Thesaurus).

Demographic data. The statistical characterization of human populations or segments of human populations; e.g., characterization by age, sex, race, or income (NCI Thesaurus).

Disposal. Systematic destruction of medical waste and other biohazardous waste (NCI Best Practices working definition).

Disposition. Transfer to the care or possession of another (Merriam-Webster Dictionary).

Distribution. 1. A process that includes receipt of request for samples, selection of appropriate samples, and final inspection, in conjunction with subsequent shipment and delivery of samples to another biospecimen resource, biospecimen collection center, or laboratory (NCI Best Practices working definition). **2.** The act of distributing, spreading, or apportioning (NCI Thesaurus).

End user. The ultimate consumer of a finished product (Merriam-Webster Dictionary).

Epidemiologic. Of or relating to epidemiology, the study of the causes, incidence and distribution of disease in the population and its application for prevention or control (NCI Thesaurus).

Extramural. 1. Related to research supported by the National Institutes of Health through a grant, contract, cooperative agreement, or other funding mechanism to an external organization (National Institute of Allergy and Infectious Diseases, Glossary of Funding and Policy Terms and Acronyms, http://www.niaid.nih.gov/ncn/glossary/). **2.** External to the National Institutes of Health (NCI Best Practices working definition).

Genomics. The study of genes and their function; the study of all or a substantial portion of the genes of an organism as a dynamic system, over time, to determine how those genes interact and influence biological pathways, networks, and physiology (Eiseman et al. 2003).

Honest broker. An individual, organization, or system acting for, or on behalf of, a covered entity to collect and provide health information to research investigators in such a manner whereby it would not be reasonably possible for the investigators or others to identify the corresponding patients-subjects directly or indirectly. The honest broker cannot be one of the investigators. The information provided to the investigators by the honest broker may incorporate linkage codes to permit information collation and/or subsequent inquiries (i.e., a "re-identification code"); however, the information linking this reidentification code to the patient's identity must be retained by the honest broker and subsequent inquiries are conducted through the honest broker (NCI Thesaurus).

Human subject. A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information (45 CFR § 46.102(f)).

Identifiable. 1. The identity of the subject is or may readily be ascertained by the investigator or associated with the information (45 CFR § 46.102(f)). **2.** Able to identify the individual; or with respect to which there is a reasonable basis to believe the information can be used to identify the individual (Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, http://privacyruleandresearch.nih.gov/pr_02.asp).

Individually identifiable health information. A subset of health information, including demographic information collected from an individual, and: (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (i) that identifies the individual; or (ii) with respect to which there is a reasonable basis to believe the information can be used to identify the individual (45 CFR § 160.103)

Informatics. An occupational discipline which unites information science with computer science. It is concerned with the development of techniques for the collection and manipulation of data, and the use of such data (NCI Thesaurus).

Informed consent. The legally effective consent of the human subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator**,** the sponsor, the institution or its agents from liability for negligence (45 CFR § 46.116(a)).

Institutional review board (IRB). An institutional review board reviews and has authority to approve, require modifications in (to secure approval), or disapprove all research activities at the institution covered by this policy. Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice (45 CFR § 46.107-109).

Intellectual property (IP). A commercially valuable product of the human intellect, in a concrete or abstract form, such as a copyrightable work, a protectable trademark, a patentable invention or a trade secret (Black's Law Dictionary).

Interoperability. The ability of two or more systems or components to exchange information and to use the information that has been exchanged (NCI Best Practices working definition).

Intramural. 1. Of or related to research conducted in Government programs headed by NIH-employed scientists (National Institute of Allergy and Infectious Diseases, Glossary of Funding and Policy Terms and Acronyms, http://www.niaid.nih.gov/ncn/glossary/). **2.** Internal to the National Cancer Institute or the National Institutes of Health (NCI Best Practices working definition).

Invention. Any art or process (way of doing or making things), machine, manufacture, design, or composition of matter, or any new and useful improvement thereof, or any variety of plant, which is or may be patentable under the patent laws of the United States (United States Patent and Trademark Office, Glossary of Terms, http://www.uspto.gov/main/glossary/index.html#i). For the purposes of the NCI Best Practices, this definition also applies to an invention which is or may be patentable under the patent laws of other countries.

Inventory. 1. A detailed, itemized list, report, or record of biospecimens in a biospecimen resource, especially a periodic survey of all stored biospecimens (NCI Best Practices working definition). **2.** The act or process of taking an inventory. (Merriam-Webster Dictionary).

Label. Any written, printed, or graphic material on or affixed to a specimen container or package (ISBER 2005).

Longitudinal data. Data derived from the assessment over a period of time of variables relating to an individual or group of individuals (NCI Best Practices working definition).

Material transfer agreement (MTA). A binding, legal agreement between the institution providing research materials (usually for unpatented biological materials) and the institution receiving materials that sets forth conditions of transfer and use, protects proprietary interests, and restricts distribution of the material (NCI Best Practices working definition).

Nomenclature. A system of words used in a particular discipline (NCI Thesaurus).

Package. A labeled carton, receptacle, or wrapper containing one or more containers and accompanying labeling material (ISBER 2005).

Paraffin-embedded. Chemically or otherwise fixed and then embedded in paraffin wax (NCI Best Practices working definition).

Patent. The right to exclude others from making, using, marketing, selling, offering for sale, or importing an invention for a specified period of time (20 years from the date of filing), granted by the Federal Government or other national government to the inventor if the invention is novel, useful, and nonobvious (NCI Best Practices working definition adapted from Black's Law Dictionary).

Patient. 1. One who is sick with, or being treated for, an illness or injury. **2.** An individual receiving medical care (Taber's Cyclopedic Medical Dictionary).

Preservation. 1. Use of chemical agents, alterations in environmental conditions, or other means during processing to prevent or retard biological or physical deterioration of a specimen (ISBER 2005). **2.** To preserve or maintain (Merriam-Webster Dictionary).

Prevalence. The total number of cases of a given disease in a specified population at a designated time. It is differentiated from "incidence," which refers to the number of new cases in the population at a given time (NCI Thesaurus).

Privacy. 1. The condition or state of being free from public attention to intrusion into or interference with one's acts or decisions (Black's Law Dictionary). **2.** The quality of being secluded from the presence or view of others; the condition of being concealed or hidden; the ability of a person to control the availability of information about and exposure of him- or herself (NCI Thesaurus).

Private information. Includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record) (45 CFR § 46.102(f)).

Procedure. A series of steps designed to result in a specific outcome when followed in order (ISBER 2005).

Process validation studies. The process of demonstrating that a specific procedure will consistently produce expected results within predetermined specifications (ISBER 2005).

Processing. Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen to inventory and labeling (ISBER 2005).

Protected health information (PHI). Individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. Protected health information excludes education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer (45 CFR § 160.103).

Proteomics. The study of the full set of proteins encoded by a genome; the study of the identities, quantities, structures, and biochemical and cellular functions of all proteins in an organism, organ, or organelle and how these properties vary in space, time, and physiological state (Eiseman et al. 2003).

Quality. 1. Conformance of a specimen or process with pre-established specifications or standards (ISBER 2005). **2.** Having a high degree of excellence or worth (NCI Best Practices working definition).

Quality assurance (QA). An integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project. Same as quality management system (QMS) (ISBER 2005).

Quality control (QC). Specific tests defined by the QA or QMS Program to be performed to monitor procurement, processing, preservation and storage, specimen quality, and test accuracy. These may include but are not limited to performance evaluations, testing, and controls used to determine accuracy

and reliability of the biospecimen resource's equipment and operational procedures as well as monitoring of the supplies, reagents, equipment, and facilities (ISBER 2005).

Quality management system (QMS). See Quality assurance (QA).

Reach-through rights. Rights claimed by the provider of materials to the recipient's discoveries where the discoveries are not covered by the provider's patent on the original material. Examples of reach-through rights required by providers in exchange for use of their material by the recipient might include ownership of recipient's discoveries, license exclusivity, or payments upon the sale of the discovery. Reach-through rights allow the provider to obtain rights in subject matter to which the provider would not otherwise have rights through its ownership or patent coverage of the material alone. Reach-through rights may give the provider an unfairly high level of compensation for the research use of the material by the recipient (NCI Best Practices working definition).

Remnant human specimen. A remnant of a specimen collected for routine clinical care or analysis that would otherwise have been discarded (Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable, http://www.fda.gov/cdrh/oivd/guidance/1588.html).

Research. Systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (45 § 46.102(d)).

Research participant. A living individual about whom a researcher obtains either (1) data through intervention or interaction with the individual, or (2) identifiable private information ("NCI Tutorial– Human Participant Protections Education for Research," http://www.fic.nih.gov/Butrum/H_Subjects/6a.pdf).

Retrieval. The removal, acquisition, recovery, harvesting, or collection of specimens (ISBER 2005).

Safety. 1. Processes, procedures, and technologies to ensure freedom from danger or harm (ISBER 2005). **2.** The condition of being safe from undergoing or causing hurt, injury, or loss (Merriam-Webster Dictionary).

Sample. 1. Portions of biospecimens (NCI Best Practices working definition). **2.** Serving as an illustration or example (Merriam-Webster Dictionary).

Silver-level compatibility. A level of caBIG™ compatibility requiring use of the architectures and vocabularies specified for the caBIG™ system. Use of these architectures and vocabularies will ensure a high level of compatibility between systems enabling interchange of scientific information (NCI Best Practices working definition). For full details, see caBIG™ Compatibility Guidelines, https://cabig.nci.nih.gov/guidelines_documentation/.

Simple Letter Agreement (SLA). Streamlined form of material transfer agreement (MTA) approved for use at the NIH. The NIH encourages the use of the SLA to facilitate exchanges between academic institutions (NCI Technology Transfer Branch glossary, http://ttb.nci.nih.gov/glossary.php).

Specimen. See Biospecimen.

Stakeholder. One that has a stake or an interest. In the context of the NCI Best Practices, the term stakeholder embraces research participant advocates in addition to scientists (NCI Best Practices working definition).

Standard operating procedures (SOPs). Established or prescribed methods to be followed routinely for the performance of designated operations or in designated situations (Merriam-Webster Dictionary).

Standard operating procedures (SOPs) manual. Written document describing in detail practices, procedures, and policies of a biospecimen resource (NCI Best Practices working definition).

Storage. 1. Maintenance of specimens for future use (ISBER 2005). **2.** Space or a place for storing (Merriam-Webster Dictionary).

Tissue. An aggregate of cells with different specialized characteristics that are organized anatomically, usually in the fixed framework of an organic matrix. The architectural organization that is maintained contributes to the performance of a specific collective function. Tissues are parts of organs. The term tissue is most often referred to in the context of solid tissue, as originating from a solid organ; however, tissue also can be defined broadly to include collections of cells and the extracellular matrix and/or intercellular substances from bodily fluids such as blood (NCI Best Practices working definition).

Uniform Biological Material Transfer Agreement (UBMTA). A Master Agreement among the NIH, universities, and other nonprofit research facilities used to expedite transfer of research materials among non-commercial entities (NCI Technology Transfer Branch glossary, http://ttb.nci.nih.gov/glossary.php). More information about the terms of the UBMTA and its signatories is available at the Association of University Technology Managers Web site (http://www.autm.net/aboutTT/aboutTT_umbta.cfm).

Unidentifiable. Tissue for which identifiable information was not collected or, if collected, was not maintained and cannot be retrieved by the repository (Eiseman et al. 2003).

Unique identifier. A code used to identify an object that is unique within a given context (NCI Best Practices working definition).

Universal precautions. The CDC publication entitled "Recommendations for Prevention of HIV Transmission in Health-Care Settings" is also known as "Universal Blood and Body Fluid Precautions" or "Universal Precautions." Under universal precautions, blood and certain body fluids of all patients are considered potentially infectious for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and other bloodborne pathogens. Universal precautions are intended to prevent parenteral, mucous membrane, and nonintact skin exposures of health-care workers to bloodborne pathogens. In addition, immunization with HBV vaccine is recommended as an important adjunct to universal precautions for health-care workers who have exposures to blood ("Perspectives in Disease Prevention and Health Promotion Update: Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and Other Bloodborne Pathogens in Health-Care Settings," http://www.cdc.gov/mmwR/preview/mmwrhtml/00000039.htm).

Use case. A detailed description of the manner in which an end user would use a system to accomplish a task they would consider important and what the system does to satisfy those needs (NCI Best Practices working definition).

ACRONYM LIST

BMBL	Biosafety in Microbiological and Biomedical Laboratories
BRN	Biospecimen Research Network
BSL	biosafety level
caBIG™	cancer Biomedical Informatics Grid
CDC	Centers for Disease Control and Prevention
CDEs	common data elements
CFR	Code of Federal Regulations
CMMI	Capability Maturity Model Integration
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
IATA	International Air Transport Association
IP	intellectual property
IRB	institutional review board
ISBER	International Society for Biological and Environmental Repositories
IT	information technology
MTA	material transfer agreement
NCI	National Cancer Institute
NCICB	National Cancer Institute Center for Bioinformatics
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OSHA	Occupational Safety and Health Administration
PHI	protected health information
QA	quality assurance
QC	quality control
QMS	quality management system
RNA	ribonucleic acid
SLA	Simple Letter of Agreement
SOPs	standard operating procedures
UBMTA	Uniform Biological Material Transfer Agreement

APPENDIX 1
NCI INFRASTRUCTURE TO SUPPORT INFORMATICS BEST PRACTICES

The NCI has identified the ability to share research data electronically as key to achieving its goal of eliminating death and suffering due to cancer. To this end, the NCI established the caBIG™ (see https://cabig.nci.nih.gov/), an infrastructure designed to facilitate the exchange of data and programs among NCI-supported Cancer Centers. NCI-supported biospecimen resources are encouraged to draw on caBIG™ to implement the informatics recommendations outlined in Section B.5 of the NCI Best Practices. Of particular relevance to NCI-supported biospecimen resources is the Tissue Banks and Pathology Tools Workspace (TBPTW) dedicated to the integration, development, and implementation of biospecimen resource and pathology tools.

Interoperability Using caBIG™

The NCI supports caBIG™ compatibility of the informatics systems used by NCI-supported biospecimen resources as a step toward integrating biospecimen resource systems with other sources and types of data from clinical research and genomic and proteomic laboratory studies.

All caBIG™ applications are open source and free of charge. While applications like caTISSUE Core and cancer Text Information Extraction System (caTIES) are developed within caBIG's™ TBPTW, use of these tools is not expected to be the only way of achieving caBIG™ compatibility. Biospecimen resources should work with the developers of their software on making these systems interoperable with others through caBIG™ compatibility.

caBIG™ Compatibility Guidelines

The caBIG™ Compatibility Guidelines provide a high-level description of requirements for interoperability (see https://cabig.nci.nih.gov/guidelines_documentation). The Guidelines are organized into four levels of maturity based on degrees of interoperability: Legacy, Bronze, Silver, and Gold. NCI-supported biospecimen resources are encouraged to establish new informatics systems that are caBIG™ compatible at the silver level and to place systems that are being replaced or upgraded on a path to silver-level compliance.

Silver-level compatibility requires that systems utilize data elements defined in a common metadata biospecimen resource, such as the cancer Data Standards Repository (caDSR) (see http://ncicbsupport.nci.nih.gov/sw/content/caDSR.html). The caDSR and its associated services provide the infrastructure to handle standardized terminologies addressed in the Guidelines. For questions or comments on the caDSR, please contact the NCICB Application Support Group via e-mail at ncicb@pop.nci.nih.gov.

APPENDIX 2
MATERIAL TRANSFER AGREEMENT FOR HUMAN SPECIMENS

This material transfer agreement (MTA) is intended for use when unidentifiable or coded human biospecimens are transferred. Transfer of human biospecimens with associated identifiable private information may require additional terms to this MTA or other documents.

Provider Organization ("Provider"): _____

Recipient Organization ("Recipient"): _____

1(a). The material to be transferred ("MATERIAL") (name or description of human specimen(s) or collections, method of preservation, organ source, etc.):

_____

_____

1(b). Designate the status of the MATERIAL (**check one below**):

__ Unidentifiable __ Coded

2. The Recipient will use the MATERIAL (**check one only**):

_____ As a biospecimen resource that will distribute the MATERIAL to the research community on behalf of the Provider under a separate MTA

_____ To conduct an independent research project (describe the "RESEARCH PROJECT" below):

_____

_____

Recipient serving as a biospecimen resource

(Articles 3-6, 12 and 13 apply to Recipients serving as a biospecimen resource.)

3. If the MATERIAL is being provided by the Provider under this Agreement for the purpose of the Recipient distributing the MATERIAL to the research community, the Provider hereby grants the Recipient explicit permission to further distribute the MATERIAL to the research community as a biospecimen resource. **Provider approval (initial here)** _____

4. If the Recipient is designated as a biospecimen resource in Article 2, the Recipient is the custodian of the MATERIAL and therefore does not by virtue of this Agreement acquire any intellectual property rights in the MATERIAL nor in any research conducted by third parties using the MATERIAL.

5. The Recipient will distribute the MATERIAL in compliance with all applicable Federal, State and local statutes and regulations which include the Common Rule (45 CFR Part 46, Subpart A) and the Health Insurance Portability and Accountability Act (HIPAA).

6. The above MATERIAL is being distributed as a service to the research community. It is acknowledged that the MATERIAL is a resource in limited quantity and that further distribution for research purposes may be determined by scientific merit of the proposed research project. Accordingly, the MATERIAL will be made available to other scientists under a separate MTA for scientifically approved projects and to the extent supplies are available.

Recipient conducting an independent Research Project

(Articles 7-13 apply to Recipients conducting an independent Research Project)

7. If the MATERIAL is being provided by the Provider under this Agreement for the purpose of the Recipient conducting an independent research project, the MATERIAL will be used only for the RESEARCH PROJECT described in Article 2 and in compliance with all applicable Federal, State and local statutes and regulations, which include the Common Rule (45 CFR Part 46, Subpart A) and HIPAA. The MATERIAL was collected and is provided in accordance with appropriate Federal and local laws, assurances, and institutional review board approvals related to human subjects research. The Recipient is responsible for obtaining any necessary human subjects research approvals or exemptions required to use the MATERIAL for the RESEARCH PROJECT.

8. The Recipient will not further distribute the MATERIAL to others who are not under the Recipient's direct supervision without written permission from the Provider. The Recipient shall refer any request for the MATERIAL to the Provider.

9. The Recipient will in no way attempt to identify or contact the person(s) from whom the MATERIAL was collected or derived. Under no circumstances will the key to coded samples be given to the Recipient under this Agreement.

10. It is intended that the Recipient publish the results of the RESEARCH PROJECT and make the associated data available to the research community in a manner consistent with the NIH Data Sharing Policy found at http://grants.nih.gov/grants/policy/data_sharing/. The Recipient agrees to acknowledge the source of the MATERIAL in any publications or disclosures reporting use of it.

11. The Recipient retains ownership of intellectual property made by its employees using the MATERIAL as part of the RESEARCH PROJECT to the extent permitted by law or contractual agreements.

All Parties Agree

12. THIS MATERIAL IS NOT FOR USE IN HUMAN SUBJECTS OR FOR THE TREATMENT OR DIAGNOSIS OF HUMAN SUBJECTS.

13. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE Provider MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Unless prohibited by law, Provider disclaims all liability for claims for damages that may arise from Recipient's use, storage, or disposal of the Material.

(signatures found on the following page)

Provider Scientist:	Name of Authorized Official:
Provider Organization:	Title of Authorized Official:
Address:	
Signature for Provider Date	Signature of Authorized Official Date

Recipient Scientist:	Name of Authorized Official:
Recipient Organization:	Title of Authorized Official:
Address:	
Signature for Provider Date	Signature of Authorized Official Date

Acknowledgement of Recipient Scientist: I have read and understood the conditions outlined in this Agreement, and I agree to abide by them in the receipt and use of the MATERIAL.

Scientist Receiving Material Date